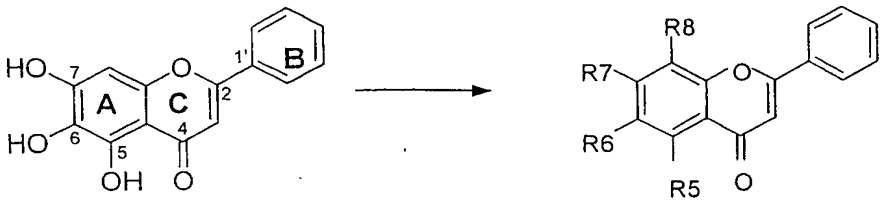
FIGURE 1 Scheme 1[a]



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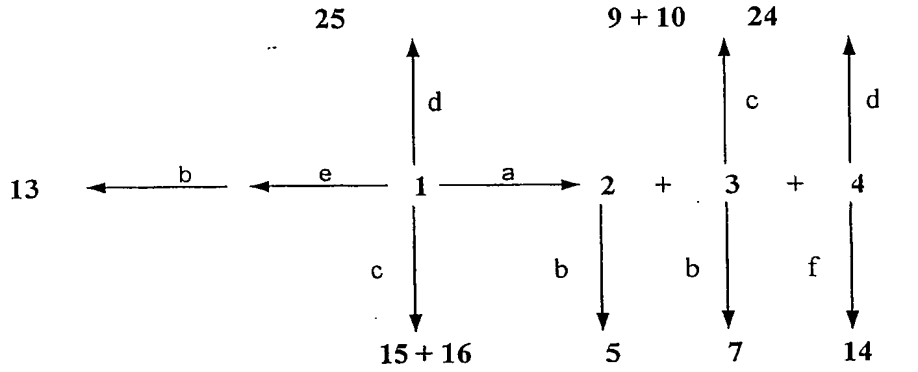

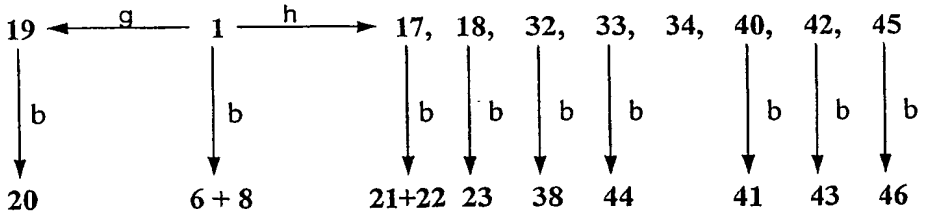

[a] Reagents and conditions: (a) Ac_2O, pyridine, rt; (b) $TMSCHN_2$, THF:MeOH (2:1), rt; (c) K_2CO_3, BnBr, acetone, reflux; (d) NBS, THF, *conc* H_2SO_4, rt; (e) Ph_2CCl_2, 170 °C; (f) K_2CO_3, KI, BnBr, acetone, reflux; (g) Cs_2CO_3, $BrCH_2Cl$, DMF, 50 °C; (h) K_2CO_3, $CH_3(CH_2)_nX$ (X=I or Br, n=1 for **32**, **33**, n=2 for **17**, **18**, n=3 for **45**, n=4 for **40**, n=5 for **42**, n=7 for **34**), acetone, reflux.

FIGURE 2

Table 1. Anti-P-gp activity and cytotoxicity of acetylated baicalein compounds.

	functional group				c log P[a]	anti-P-gp activity[b]		cytotoxicity $IC_{50}(\mu M)$[e]	
compd	R5	R6	R7	R8		EC_{50} (μM)[d]	A_{max}[c]	KB	KB/MDR
control							0.5±0.1[f]		
CSA					2.9	1.2±0.3	3.5±0.3	0.6±0.2	1.5±0.7
VRM					4.5	14±1.2	2.2±0.1	19.6±2.7	51.7±4.7
1	OH	OH	OH	H	3.0	41±5.1	1.7±0.1	62.3±3.7	87.1±3.6
2	OH	OAc	OH	H	2.5	11±2.1	3.1±0.2	10.5±1.4	61.6±4.8
3	OH	OAc	OAc	H	2.4	9.7±1.8	2.6±0.1	12.7±2.3	69.3±6.4
4	OAc	OAc	OAc	H	1.2	6.8±0.7	3.0±0.2	14.5±2.1	57.2±7.3
7	OMe	OAc	OAc	H	1.7	12.3±1.5	2.9±0.1	> 100	>100
5	OMe	OAc	OMe	H	2.3	11.5±1.1	2.4±0.1	85.5±8.5	>100
24	OH	OAc	OAc	Br	3.1	15±3.1	1.8±0.3	12.4±2.7	16.2±2.3
25	OH	OH	OH	Br	3.7	15±2.9	1.8±0.2	14.1±1.4	18.7±3.1

Ac = acetyl and Me = methyl.

FIGURE 3

Table 2. Anti-P-gp activity and cytotoxicity of benzylated baicalein compounds.

	functional group				c log P	anti-P-gp activity[b]		cytotoxicity IC_{50}(μM)[e]	
compd	R5	R6	R7	R8		EC_{50} (μM)[d]	A_{max}[c]	KB	KB/MDR
control							0.5±0.1[f]		
CSA					2.9	1.2±0.3	3.5±0.3	0.6±0.2	1.5±0.7
VRM					4.5	14±1.2	2.2±0.1	19.6±2.7	51.7±4.7
1	OH	OH	OH	H	3.0	41±5.1	1.7±0.1	62.3±3.7	87.1±3.6
9	OBn	OAc	OAc	H	3.5	3.7±0.2	3.6±0.2	11.3±1.7	12.2±1.1
10	OH	OBn	OAc	H	4.7	2.4±0.1	2.8±0.1	16.3±2.1	18.3±2.3
14	OAc	OAc	OBn	H	3.5	1.1±0.1	3.4±0.2	13.4±2.4	13.7±2.1
15	OH	OBn	OH	H	4.8	1.8±0.1	3.7±0.2	4.3±1.6	3.2±1.2
16	OH	OBn	OBn	H	7.1	70±5.4	1.1±0.1	> 100	>100
13	OMe	$OCPh_2O$		H	6.7	11.5±2.2	1.9±0.1	60.5±5.5	40.6±3.4

Bn = benzyl, Me = methyl, and Ph = phenyl.

FIGURE 4

Table 3. Anti-P-gp activity and cytotoxicity of alkylated baicalein compounds.

	functional group				c log P[a]	anti-P-gp activity[b]		cytotoxicity $IC_{50}(\mu M)$[e]	
compd	R5	R6	R7	R8		EC_{50} (μM)[d]	A_{max}[c]	KB	KB/MDR
control							0.5±0.1[f]		
CSA					2.9	1.2±0.3	3.5±0.3	0.6±0.2	1.5±0.7
VRM					4.5	14±1.2	2.2±0.1	19.6±2.7	51.7±4.7
1	OH	OH	OH	H	3.0	41±5.1	1.7±0.1	62.3±3.7	87.1±3.6
8	OH	OMe	OMe	H	3.5	4.6±1.1	3.4±0.3	> 100	>100
6	OMe	OMe	OMe	H	2.9	5.5±0.4	2.7±0.2	85.9±7.8	57.9±5.9
19	OH	OCH_2O		H	3.7	6.5±1.3	1.2±0.1	> 100	>100
20	OMe	OCH_2O		H	3.1	4.4±2.1	1.5±0.1	> 100	>100
32	OH	OEt	OH	H	3.6	2.3±0.3	3.5±0.3	24.6±3.5	17.5±5.6
38	OH	OEt	OMe	H	4.1	1.5±0.3	2.3±0.2	> 100	>100
33	OH	OEt	OEt	H	4.6	1.8±0.2	4.9±0.2	> 100	>100
44	OMe	OEt	OEt	H	3.9	1.1±0.1	4.2±1.1	81.7±7.8	79.2±5.8
17	OH	OPr	OH	H	4.1	2±0.7	4.7±0.1	58.9±6.3	>100
21	OH	OPr	OMe	H	4.6	1.2±0.4	4.6±0.1	> 100	>100
22	OMe	OPr	OMe	H	3.9	1.7±0.1	4.6±0.1	>100	>100
18	OH	OPr	OPr	H	5.6	1.4±0.4	5.0±0.2	> 100	>100
23	OMe	OPr	OPr	H	5.0	0.9±0.1	5.2±0.1	86.4±6.3	93.7±2.2
45	OH	OC_4H_9	OC_4H_9	H	6.7	1.5±0.3	3.2±0.1	> 100	>100
46	OMe	OC_4H_9	OC_4H_9	H	6.1	1.6±0.2	4.4±0.1	> 100	>100
40	OH	OC_5H_{11}	OC_5H_{11}	H	7.8	1.8±0.1	1.1±0.1	> 100	>100
41	OMe	OC_5H_{11}	OC_5H_{11}	H	7.1	1.5±0.1	3.2±0.1	75.4±6.4	82.6±8.4
42	OH	OC_6H_{13}	OC_6H_{13}	H	8.8	1±0.1	1.0±0.1	> 100	>100
43	OMe	OC_6H_{13}	OC_6H_{13}	H	8.2	1.3±0.2	1.1±0.1	39.1±8.5	44.8±7.9
34	OH	OC_8H_{17}	OC_8H_{17}	H	10.9	7.4±4.1	1.2±0.1	> 100	>100

Me = methyl, Et = ethyl, Pr = *n*-propyl and Ph = phenyl.